

## DEVELOPMENTAL GENETICS

# The making of a male

The discovery of the role of Sry in male development was heralded as a great breakthrough and it became known as a classic master switch of development: XY vertebrates with functional Sry developed as males; those without it developed as females. Despite the initial excitement, however, working out what was upstream and downstream of this transcription factor proved very difficult. Luis Parada and colleagues have just made an important step towards solving this mystery — they show that the insulin receptor tyrosine kinase family is required for male sexual differentiation in mice, and that it functions early in development, probably upstream of *Sry*.

The insulin family signalling pathway comprises three receptors: Ir, Igf1r and Irr. Single mouse mutants at these loci do not show any abnormal sexual phenotype but, as the authors show by electron microscopy and histochemical analysis, XY triple mutants are completely feminized. *In situ* hybridization confirmed these findings — no testis-specific genes were expressed in the XY triple mutants, although ovary-specific gene expression was normal. The three insulin receptors must act early in the sex differentiation pathway as expression of early male-specific markers such as *Sox9* and *Mis* was reduced and absent, respectively, in the XY triple-mutant embryos. At the same time, female-specific expression of *Wnt4* was upregulated.

Perhaps it is not surprising then, that *Sry* expression was also reduced. The authors concluded that this reduction was caused by a

slower rate of cell proliferation in the testis in the triple mutants, which led to the presence of fewer *Sry*-expressing Sertoli-cell precursors.

Although it was only the triple mutants that were completely feminized, by looking at various double-mutant combinations, Parada and colleagues showed that there is functional redundancy among the three insulin receptors and that these can be ranked according to the strength of their effects — Igf1r having the strongest effect on the phenotype and Irr the weakest.

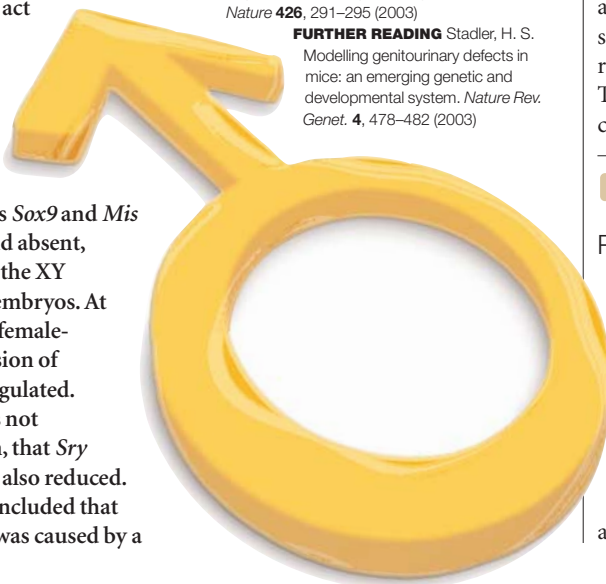
Despite the fact that sex-determination mechanisms evolve rapidly, there is some degree of conservation in the pathways involved between invertebrates and vertebrates. As the insulin-signalling pathway is also present in worms and flies, Parada and colleagues call for using these organisms to identify further potential candidates in this pathway that have a role in male differentiation.

Magdalena Skipper

## References and links

**ORIGINAL RESEARCH PAPER** Nef, S. & Verma-Kurvari, S. *et al.* Testis determination requires insulin receptor family function in mice. *Nature* **426**, 291–295 (2003)

**FURTHER READING** Stadler, H. S. Modelling genitourinary defects in mice: an emerging genetic and developmental system. *Nature Rev. Genet.* **4**, 478–482 (2003)



## IN BRIEF

### GENOMICS

The genome sequence of *Caenorhabditis briggsae*: a platform for comparative genomics.

Stein, L. D. *et al.* *PLoS Biology* **1**, 166–192 (2003)

A high-quality draft sequence of the nematode *Caenorhabditis briggsae*, a close relative of *C. elegans*, is now available. 12,200 of its 19,500 protein coding genes have clear *C. elegans* orthologues. The 104 Mb genome is slightly larger than that of *C. elegans*, mainly owing to repeat families, few of which are shared between the species. Apart from providing a wealth of information about *C. briggsae*, this genome sequence will greatly improve genome annotation of its more widely used cousin.

### GENOME EVOLUTION

Evolutionary discrimination of mammalian conserved non-genic sequences (CNGs).

Dermitzakis, E. T. *et al.* *Science* **302**, 1033–1035 (2003)

Following on from the observation that most conserved sequences between mouse and human genomes are probably non-coding, Dermitzakis and colleagues have compared the evolutionary properties of 191 human–mouse conserved non-genic sequences (CNGs) across 14 mammalian species. Surprisingly, CNGs are more highly conserved than non-coding RNAs or protein coding genes; instead, they seem to be constrained in a way that is more similar to protein binding regions.

### TECHNOLOGY

Array-based comparative genomic hybridization for the genomewide detection of submicroscopic chromosomal abnormalities.

Vissers, L. E. L. M. *et al.* *Am. J. Hum. Genet.* **73**, 1261–1270 (2003)

Microdeletions and microduplications often underlie mental retardation and human malformations, but are difficult to identify because they not visible using routine chromosome analysis. The authors devised and tested a high-resolution screening procedure in which differentially labelled test and reference DNAs are hybridized to arrays of genomic clones. The results show that deletions and duplications as small as 1 Mb can be reliably detected using this method.

### EVOLUTION

Positive selection on a human-specific transcription factor binding site regulating *IL4* expression.

Rockman, M. V. *et al.* *Curr. Biol.* **13**, 2118–2123 (2003)

A SNP in the promoter of the immune cytokine interleukin-4 (IL-4) determines how effectively the transcriptional activator NFAT binds. Rockman and colleagues show that the T variant of the SNP — which creates a ‘hair-trigger’ for IL-4 transcription — has been driven to high frequencies in some populations by positive selection, possibly to facilitate an adaptive immune response to extracellular pathogens.